

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO MUSTARD GAS IN THE UNITED STATES

Mustard gas does not naturally occur, and, therefore, there are no background levels in the soil, air, water, or food. Mustard gas is a chemical warfare agent. Its use has been confirmed in World War I and in the Iran-Iraq War, and there are reports of mustard gas being utilized in other conflicts. The production of mustard gas in the United States was discontinued in the mid-1950s. Since mustard gas is no longer produced or used commercially in the United States, occupational and general population exposures are expected to be low. The U.S. stockpile of mustard gas is currently stored at seven sites in the continental United States and one site located on Johnston Island in the Pacific Ocean. If mustard gas is accidentally released into the air, the primary routes of exposure would be inhalation or contact with eyes and skin. Mustard gas has been found in at least 3 of the 1,585 current or former NPL sites. At hazardous waste sites, exposure to mustard gas is also possible by dermal contact with contaminated soil or containers. Children are expected to be exposed to mustard gas by the same routes as adults.

2.2 SUMMARY OF HEALTH EFFECTS

Numerous reports of combat exposures to mustard gas provide strong evidence of the toxic potential of mustard gas. Additional information on the health effects of mustard gas is available from studies of mustard gas factory workers and mustard gas testing of volunteers. As summarized below and detailed in Chapter 3, effects that have been associated with exposure to mustard gas in humans and/or animals include ocular and dermal injury, respiratory tract irritation, reproductive and developmental toxicity, gastrointestinal effects, hormone alterations, hematological and lymphoreticular effects, and cancer. Combat mustard gas exposure levels have not been quantified, and blast effects may be present concurrently. Studies of mustard gas workers are complicated by possible concurrent exposure to other toxic agents because factories generally produced multiple chemical warfare agents. The lack of follow-up health assessments of human subjects in gas chamber and field tests limits the assessment of long-term health consequences. Therefore, available human data are not appropriate for quantitative risk assessments. Animal studies have shown that mustard gas induces similar toxic effects in animals and humans, with the exception of blistering of animals that have fur. However, most animal studies have been conducted with mustard gas administered by oral or intravenous routes.

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Direct Contact Effects. Data from soldiers and civilians exposed during combat, mustard gas factory workers, mustard gas testing volunteers, and accidental exposures provide ample evidence of the toxic potential of mustard gas to tissues coming into direct contact with mustard gas. Mustard gas exposure results in eye irritation and burning of the skin, which begins several hours after exposure. The severity of cutaneous injury is dose- and temperature-dependent and is directly related to the mustard gas alkylation levels in skin. It is likely that direct contact with other tissues would have these same dependencies. Due to the aqueous nature and accessibility, the eyes are more sensitive to mustard gas than the skin or respiratory tract. The damage may vary from mild conjunctivitis to severe corneal involvement with dense opacification, ulceration, and vascularization. Delayed ocular reactions, manifested as delayed relapsing keratitis, may also occur. Early respiratory effects include shortness of breath, a burning sensation of the vocal cords, and hemorrhagic inflammation of the tracheobronchial mucosa accompanied by severe erosions or membranous lesions. Children appear to be more sensitive to the irritant effects of mustard gas with manifestations of exposure occurring as early as 4 hours after exposure, whereas effects in adults are generally delayed by at least 8 hours. In children, cough was the first respiratory symptom. Breathing pattern alterations and erosions of the airway mucosa have also been reported in animals. Prolonged inhalation exposure can result in chronic bronchitis or cancer of the respiratory passages and lungs. Stomach irritation and inflammation and bleeding of the gastric mucosa were reported in victims of combat exposure where at least small amounts were likely ingested. Similar effects have been observed in animal studies.

Reproductive Effects. While the routes of exposure differ, animal reproductive effects data support the long-term effects reported in humans. In a follow-up study of men who were injured by mustard gas during the Iran-Iraq War, reduced sperm counts were reported. An increased rate of fetal deaths and an altered sex ratio were reported in progenies of Iranian survivors of chemical attacks that included mustard gas. An increase in fetal mortality also occurred in an animal study subsequent to the mating of orally exposed male and unexposed female rats. Altered sex ratios have been reported in a study in rats orally exposed to mustard gas. Abnormal sperms shapes were observed in rats exposed to mustard gas by the oral route. The reproductive effects appear to be male dominant as no changes were seen in the number of live fetuses or resorptions in a study of pregnant rats exposed to mustard gas in the air.

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Developmental Effects. An increased incidence of congenital malformations (skeletal and muscle abnormalities, limb defects, anacephaly, hydrocephaly, microcephaly, cleft lip and palate, deafness, blindness, and mental retardation) was reported among offspring of Iranian mustard gas victims. The study could not distinguish whether the observed defects were caused only by exposure to chemical agents or by other environmental factors as well. In animal fetuses, incidences of reduced ossification and reduced body weight have occurred when the mother was exposed to mustard gas doses that produced maternal toxicity.

Cancer. There is sufficient evidence that mustard gas is carcinogenic to humans. Epidemiological studies on World War I victims exposed to mustard gas revealed an association between respiratory exposure and the risk of developing lung cancer. Factory workers exposed to mustard gas for a number of years have been shown to develop respiratory cancer. Although most human studies have found an association between mustard gas exposure and respiratory cancer, some studies have not found a significant relationship, possibly due to lower exposure levels. It is also documented that occupational dermal exposure to mustard gas produces Bowen's diseases (precancerous dermatitis) in humans. Two animal studies, of low predictive quality due to species strain tendency to develop lung tumors, insufficient animals, and inadequate doses, have also shown increases in tumors from mustard gas exposure in the air. Subcutaneous, intramuscular, and intravenous injections of mustard gas into mice have also produced increased tumors at the site of the injection, in the mammary glands, or in the lungs.

2.3 MINIMAL RISK LEVELS (MRLs)

The details regarding calculations of the MRLs for mustard gas are described in Appendix A.

Inhalation MRLs

CAAn MRL of 0.0002 mg/m³ has been derived for acute-duration inhalation exposure (14 days or less) to mustard gas.

There are numerous reports of exposure to mustard gas during combat and in mustard gas factories; however, the exposure levels or durations were not quantified, and therefore, these data are inadequate for deriving dose-response relationships. The acute-duration inhalation MRL was based on a lowest-observed-adverse-effect level (LOAEL) of 21.3 mg/m³ for respiratory effects in mice that were exposed

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for 1 hour. The LOAEL was duration-adjusted to a 24-hour exposure period and dosimetrically adjusted for humans, and an uncertainty factor of 300 [10 for use of a LOAEL, 3 for extrapolation from animals to humans using a dosimetric adjustment, and 10 for human variability] and a modifying factor of 3 [for proximity to serious effects (28% body weight loss at 16.9 mg/m³)] were applied to the LOAEL to derive the MRL (see Appendix A for details). Groups of female Swiss albino mice were administered 8.5, 16.9, 21.3, 26.8, 42.3, or 84.7 mg/m³ of mustard gas by inhalation for 1 hour. At all mustard gas concentrations, mice exhibited reversible sensory irritation, characterized by a pause between inspiration and expiration, and the respiratory frequency decreased to a slower steady state after 30 minutes of exposure. While sensory irritation was reversible (normal respiration pattern was recovered after inhalation exposure was terminated), delayed effects of mustard gas were indicated by a significant reduction in respiratory frequency beginning 48 hours after exposure at concentrations of ≥ 21.3 mg/m³. The depression in respiratory frequency following exposure was related to both concentration and postexposure time. Airflow limitation, evidenced by the decreased respiratory rate, is thought to occur due to the effect of mustard gas on the tracheal secretory cells. In addition to the respiratory effects, significant ($\geq 25\%$) reductions in body weight occurred at ≥ 16.9 mg/m³ at 7 days postexposure; however, the magnitude of the weight reduction at 16.9 mg/m³ (28%) was greater than that observed in two other studies in mice and guinea pigs in which weight reductions of only 14% were reported at 85 and 125 mg/m³, respectively, at similar postexposure times. ATSDR considers the respiratory system to be the critical target for acute toxic effects of mustard gas, and the concentration of 21.3 mg/m³ to be a LOAEL for delayed respiratory effects beginning 48 hours after exposure, for derivation of an acute-duration inhalation MRL.

There is ample evidence of mustard gas-induced respiratory effects in humans following acute and chronic exposures. Soldiers reported shortness of breath and early respiratory manifestations including hemorrhagic inflammation of the tracheobronchial mucosa accompanied by severe erosions or membranous lesions. Some exposed soldiers became temporarily aphonic due to an acid-like burning sensation of the vocal cords. Coughing was the first respiratory symptom in children. Secondary complications consisted of extensive stenosis of sections or the entire tracheobronchial tree, suppurative bronchitis, and chronic respiratory infections. Scars, ulcers, strictures, and nonspecific fibrous granulation developed in central airways after a delay of up to 15 months. Progressive deterioration of lung compliance and gas exchange with resulting hypoxemia and hypercapnia were common with injury. Chronic respiratory complaints included shortness of breath, chest tightness, cough, sneezing, rhinorrhea, and sore throats. Long-term or delayed effects included central airway stenosis, bronchiectasis, bronchiolitis, and bronchitis.

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Other studies show that factory workers who were apparently exposed to mustard gas for a few years developed acute and chronic respiratory effects. Factory workers in Britain who were exposed to mustard gas also showed increased deaths due to acute and chronic nonmalignant respiratory disease, including influenza and pneumonia. Workers in a Japanese poison gas factory were more likely to have chronic bronchitis, chronic cough, and decreased respiratory volume than nonexposed persons. A significantly increased incidence of mortality from pneumonia was reported among 428 former workers of a mustard gas manufacturing facility.

Short-term respiratory effects similar to those described in humans have been reported in experimental animals. Microscopic changes of the airways and lungs were observed in rabbits and dogs exposed to mustard gas vapor. The major pathological changes were in the nasal passages, pharynx, larynx, and upper portion of the respiratory tract. In animals with severe injuries that survived beyond a few days, the lesions incurred secondary infections, as in humans, leading to bronchopneumonia, which apparently was the cause of death in many cases. Subsequent to acute (#1 hour) inhalation exposure, a decrease in respiratory rate that lasted for up to 7 days after exposure was reported in mice and guinea pigs.

CMRLs for intermediate- (15–364 days) and chronic-duration (364 days or more) inhalation exposure to mustard gas have not been derived because quantitative data were not available to determine no-observed-adverse-effect levels (NOAELs) or LOAELs.

Oral MRLs

CAn MRL of 0.0005 mg/kg/day (0.5 µg/kg/day) has been derived for acute-duration oral exposure (14 days or less) to mustard gas.

The acute-duration oral MRL was based on a LOAEL of 0.5 mg/kg/day for inflamed mesenteric lymph nodes in rat dams administered mustard gas by intragastric intubation. The dose is also a LOAEL for reduced ossification in the fetuses. An uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) was applied to the LOAEL to derive the MRL. There were no treatment-related deaths in groups of 25–27 mated Sprague-Dawley female rats (10–11 weeks old) that were dosed acutely on gestation days 6–15 (10 days) with 0, 0.5, 1.0, or 2.0 mg/kg/day mustard gas (95.9–96.1% purity) in sesame oil in a teratology study. Significant incidences of inflamed mesenteric lymph nodes in dams and reduced ossification in fetuses occurred with mustard gas doses \geq 0.5 mg/kg/day (see Appendix A for additional details).

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There is some evidence for mustard gas-induced lymph system effects in humans. Lymph node discoloration and spleen pathology were found in autopsies of mustard gas victims. Additional studies in animals also indicate mustard gas-induced damage to the lymph system. Incidences of inflamed mesenteric lymph nodes occurred at \$0.4 mg/kg/day in dose-range experiments and another lymphoretic effect, enlarged Peyer's patches, was observed in rabbits at 0.5 mg/kg/day in a range-finding study and at 0.4 mg/kg/day in a teratology study (incidence data not reported).

CAn MRL of 0.00002 mg/kg/day (0.02 µg/kg/day) has been derived for intermediate-duration oral exposure (15–364 days) to mustard gas.

The intermediate-duration oral MRL was based on a dose of 0.03 mg/kg/day for gastrointestinal effects in rats administered mustard gas by intragastric intubation. The corresponding time-weighted average LOAEL used in the MRL derivation was 0.02 mg/kg/day (see Appendix A for details). An uncertainty factor of 1,000 was applied to the LOAEL to derive the MRL. In a two-generation reproduction study, groups of 8-week-old Sprague-Dawley rats (27 female and 20 males/group/generation) were dosed with 0, 0.03, 0.1, or 0.4 mg/kg/day mustard gas (97.3% purity) in sesame oil. Male and female rats were dosed 5 days/week for 13 weeks before mating and during a 2-week mating period. Males were dosed 5 days/week during the 21-day gestation period. Females were dosed daily (7 days/week) throughout the 21-day gestation period and 4–5 days/week during the 21-day lactation period. Mated males were sacrificed at the birth of their pups, and dams were sacrificed when their pups were weaned. Male and female F1 pups were treated with mustard gas until they were mated and the females became pregnant and gave birth. The dosing of F1 dams continued until pup weaning, at which time, the study was terminated. Significant dose-related incidence and severity of hyperplasia of the squamous epithelium of the forestomach occurred in both sexes with mustard gas doses \$0.03 mg/kg/day (see Appendix A for additional details).

In support of the critical effect, gastrointestinal effects have been reported in humans following combat exposure to mustard gas, in mustard gas testing volunteers, and in mustard gas factory workers. Gastrointestinal effects (edema, hemorrhage or sloughing of the mucosa, and ulceration) were also observed in rabbits following 14-day exposures at \$0.4 mg/kg/day, in rats following 10-day exposures at \$2.0 mg/kg/day, and in rats following 13-week exposures at \$0.1 mg/kg/day.

CAn MRL for chronic-duration oral exposure (364 days or more) to mustard gas has not been derived because quantitative data were not available to determine NOAELs or LOAELs.

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No studies were located regarding the toxicity of mustard gas in humans or animals following chronic oral exposure.